Remarks

Claim Amendments

The independent claims have been amended to specify one particular nucleotide analog moiety (γ-S-ATP) and one particular tether (an acetamide group). These amendments are supported *inter alia* by original claims 3, 72, and 73.

Other claims have been cancelled as redundant or inconsistent with the amended independent claims.

New claims 77-88 have been added. These claims are supported in the specification as shown in detail below. These claims are directed to methods of making the inhibitors of the examined claims and to the inhibitors themselves.

Claim	Element	Support in Specification as published in US 2002/0031820
77, 78	Synthesizing a peptide comprising a nitrophenylalanine residue	[0035], lines 1-5
77, 78	Reducing the nitro group	[0035], lines 5-6
	Bromoacetylating the amine group	[0035], lines 6-7
77,78	Displacing the bromide group	[0035], lines 10-13
78	Synthesizing a peptide comprising a a diamino proprionic acid residue	[0055], lines 10-14
78	Reducing the nitro group	[0035], lines 5-6
78	Bromoacetylating the amine group	[0035], lines 6-7; [0055], lines 27-41
78	Displacing the bromide group	[0035], lines 10-13; [0055], lines 41-43
79	Peptide is a Markush group	[0023], lines 8-9, 13-17
83	Peptide is a Markush group	[0023], lines 8-9, 13-17, and [0023], lines 9-12, 13-17
80, 84	Assaying to determine potency	[0038-41] and [0057]
81, 85	Assaying to determine specificity	[0042] and [0058], lines 30-33
82, 86	Known phosphorylation sites for kinase enzymes with particular recited substitutions	[0023], lines 6-13; and [0024]
87	An inhibitor	Claim 1; and [0023]
88	An inhibitor	Claim 60; and [0023]

No new matter is added by these claim amendments.

The Rejection of Claims 1, 4-15, 58, 60, 63, 66-67, and 69-76 Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 4-15, 58, 60, 63, 66-67, and 69-76 stand newly rejected under 35 U.S.C. § 112, second paragraph as indefinite.

Claims 1 and 60 are allegedly indefinite in the recitation of a "nucleotide analog." Claims 1 and 60 have been amended to specify that the nucleotide analog consists of γ-S-ATP. It is respectfully submitted that this qualification removes any ambiguity.

Claims 8 and 9 were allegedly indefinite. Because they have now been cancelled, the rejection is moot.

Claim 15 is allegedly unclear in the recitation of Compound 2. Compound 2 is described in the Brief Description Of The Drawings with regard to Figure 1A. In the drawing itself, the compound is denoted with the numeral "2."

Claims 69-71 and 74 are allegedly indefinite in the use of the term "natural substrate." This term is used to mean a physiological substrate found in the same cells as the protein kinase. The natural substrate or physiological substrate is a protein. The term "unnatural substrate" does not appear to be used in the claims.

Claims 1-14, 58, 60, 63, 66-67, 69-71, and 74-76 are allegedly unclear in the description of the tether. The description of the tether has been changed in independent claims 1 and 60 so that a particular chemical moiety is recited rather than one with a particular size. It is respectfully submitted that this amendment obviates the rejection.

Withdrawal of this rejection is respectfully requested in view of the claim amendments.

The Rejection of Claims 1-14, 58, 60, 63, 66-67, and 69-76 Under 35 U.S.C. § 112, First Paragraph

Claims 1-14, 58, 60, 63, 66-67, and 69-76 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an adequate written description. In particular the rejection asserts that the application fails to disclose a representative number of species for the claimed genus of bisubstrate inhibitors of insulin receptor

kinase or the claimed genus of bisubstrate inhibitors of protein kinases. Applicants respectfully traverse this rejection.

To satisfy the written description requirement for a claimed genus, the specification may describe a representative number of species (1) by actual reduction to practice, (2) by reduction to drawings, or (3) by disclosure of relevant identifying characteristics sufficient to show the applicant was in possession of the claimed genus. Manual of Patent Examining Procedure § 2163(II)(A)(3)(a)(ii). Relevant identifying characteristics can be, for example, structure or other physical and/or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics. *Id.* A representative number of species is inversely related to the skill and knowledge in the art. *Id.* The specification need only describe in detail that which is new or not conventional. *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

The specification is said to insufficiently describe the claimed invention with respect to the nucleotide or nucleotide analog moiety, the tether, and the peptide. The claims have been amended so that a particular nucleotide analog moiety and a particular tether are recited. It is respectfully submitted that each of these elements of the claims are fully and adequately described in the specification.

The remaining recitation at issue is "a peptide moiety which is a substrate for said... kinase." The Office Action urges that "there is no disclosed structure-function relationship between the structure of the peptide moiety and its 'function' as being a substrate for any IRK or any protein kinase." In fact, the prior art teaches sequence motifs of substrates for insulin receptor kinase and other protein kinases. Insulin receptor kinase (IRK) is a tyrosine phosphorylase. Peptides which have YMXM motifs are taught as excellent substrates for IRK. *See* Shoelsen *et al., Proc. Natl. Acad. Sciences* 89:2027-2031, 1992; of record. This same motif makes excellent substrates for tyrosine protein kinases v-Src and v-Abl. *See* Garcia *et al., J. Biol. Chem.,* 268:25146-25151, 1993; of record. Acidic residues N-terminal to the tyrosine residue are taught to be frequent in substrates of IRK and other protein tyrosine kinases. *See* Hubbard, *EMBO J.,* 16:5573-5581, 1997; of record. Protein kinase casein kinase-2 is known to have a minimum consensus for its peptide substrate of S/T-x-x-E/D/S(P)/T(P). *See* Marin, *J. Biol. Chem.,*

274: 29260-29265, 1999; of record. Protein kinase Chk1 has a known protein phosphorylation motif of Φ-x-β-x-x-S/T. Φ is a hydrophobic residue (M>I>K>V), β is a basic residue (R>K) and x is any amino acid. *See* Hutchins, *et al., FEBS Letters,* 466:91-95, 2000; of record. The binding motif for protein kinase CaMKI is Φ-x-β-x-x-(S/T)-x-x-x- Φ. *See,* Hutchins, *supra.* An optimum sequence for peptide substrates of the protein tyrosine kinase Abl contains the sequence Ile-Tyr-Ala-Xaa-Pro. *See,* Till *et al., J. Biol. Chem.,* 274: 4995-5003, 1999; of record. Protein kinases c-Src and Hck display strikingly similar patterns of preference for substrate peptides as taught by Sicilia, *et al., J. Biol. Chem.,*273: 16756-16763, 1998; of record. The tripeptide moiety EYL is a consensus sequence for the phosphorylation site of natural substrates of EGF-R. This sequence is also found in the major autophosphorylation site. *See* Rosse, *et al., Helvetica Chimica Acta,* 80: 653-670, 1997; of record. Protein kinase CDK5 phosphorylates serine/threonine in S/T-P-X-K/R -type motifs like other CDKs. *See* Sharma *et al., J. Biol. Chem.,* 274:9600-9609, 1999; of record. Thus the prior art teaches a correlation between structure (sequence) and function of peptide substrates of protein kinases generically and of IRK in particular.

In addition to the consensus motifs taught in the prior art, Applicants have previously made of record the prior art teachings of at least 19 specific peptide substrates of IRK and at least 82 specific peptide substrates of other protein kinases. Because the prior art disclosed such a multitude of these peptide substrates, it is clear that the applicants were in possession of them. An applicant need not teach, and preferably does not burden his application with that which is known in the art. *See Hybritech, supra.* The Court of Customs and Patent Appeals explained why it was preferable to leave such known information out of an application:

> The alternative places upon patent applicants, the Patent Office, and the public the undue burden of listing in the case of applicants, reading and examining, in the case of the Patent Office, and printing and storing, in the case of the public, descriptions of the very many structural or functional equivalents of disclosed elements or steps which are already stored in the minds of those skilled in the arts, ready for instant recall upon reading the descriptions of specific elements or steps.

In re Smythe, 178 U.S.P.Q. 279, 285, (C.C.P.A.1973).

Moreover, when elements of a claim are readily available to those of ordinary skill in the art, then they need not be described in the same way as if they were new and previously unknown. As stated by the Court of Customs and Patent Appeals:

> In sum, claims drawn to the use of *known* chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description. In *Feutterer* and here, such is the case.

In re Herschler, 591 F.2d, 693, 702 (C.C.P.A. 1979).

It is respectfully submitted that the large number of known species of peptide substrates and the known definition of structural motifs demonstrate that both the art and the applicants were in possession of a genus described by structure correlated with function. The peptides are representative species of the genus of peptide substrate moieties. Applicants request that the PTO reconsider the issue of written description in view of the scope of the claims as now amended. It is respectfully submitted that the applicants have described the invention in a way that those of skill in the art would readily recognize that applicants were in possession of the invention.

New claims 77-88 do not recite a peptide which is a substrate for a kinase, but simply recite a peptide. Because the inhibitors comprise a known substrate moiety of kinases, *i.e.,* ATP, they are inherently inhibitors of kinases. The peptide, depending on its composition, may provide additional potency or specificity to the bisubstrate inhibitor. It is respectfully submitted that the genus of peptides is amply known in the art and that the PTO does not need to have further demonstration that this is the case.

<u>The Rejection of Claims 1-14, 58, 60, 63, 66, 67, and 69-76 Under 35 U.S.C. § 112, First Paragraph</u>

Claims 1-14, 58, 60, 63, 66, 67, and 69-76 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to enable the genus of bisubstrate inhibitors of insulin receptor kinase and protein kinases. In particular, the PTO urges that undue

experimentation would be required to practice the genus of bisubstrate inhibitors of protein kinase and the genus of bisubstrate inhibitors of insulin receptor kinase. Applicants respectfully traverse this rejection. The PTO acknowledges that Compound 2 is adequately enabled by the specification.

An analysis of whether a claim is enabled by the specification requires a determination of whether the specification contains sufficient information, together with knowledge in the prior art, to enable one skilled in the art to make and use the claimed invention without undue experimentation. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Factors that may be considered in determining whether experimentation is undue include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The specification need only describe in detail that which is new or not conventional. *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

The Breadth of the Claims

The claims have been amended so that the scope of the claims is considerably narrower. The only element of the claim which has not been specified structurally is the identity of the peptide moiety. The claims recite "a peptide moiety which is a substrate for said insulin receptor kinase" or "a peptide moiety which is a substrate for said protein kinase."

The State of the Prior Art

A host of both natural (physiological) and non-natural (non-physiological) peptide substrates were known in the art. Applicants identified in prior responses nineteen peptides that were known in the art to be natural peptide substrates of insulin receptor kinase or modified natural peptide substrates that were known to function as substrates of the insulin receptor kinase. Eighty-two additional peptides also were identified that were

known in the art to be substrates of protein kinases. Thus, a skilled worker would only need to select from the known natural or modified natural peptide substrates. The state of the prior art was advanced at the time of filing with regard to the components for making the inhibitors of the invention.

The Skill in the Art

The level of one of ordinary skill was high at the time applicants filed their patent application. The skilled worker in the field was a protein chemist or biochemist. Such persons typically have a Ph.D. degree with several years of post-doctoral training. Such persons would have knowledge of the art-disclosed natural and modified natural peptide substrates, or be able to find them using simple automated literature searches.

Level of Predictability

Because the prior art was rich and the skill level in the art was high, the level of predictability for making the compounds of the present invention would also have been high. No reasons have been put forward by the PTO why the elements of the claimed compounds could not have been predictably joined. No reasons have been put forward why such joined components should not function in the intended manner. In fact, the previously submitted Declaration of Dr. Philip Cole presents five additional examples where the assembled components of bisubstrate inhibitors do function in the intended manner. Such actual evidence of success rebuts mere speculation that the invention *may* not work.

Quantity of Experimentation Needed

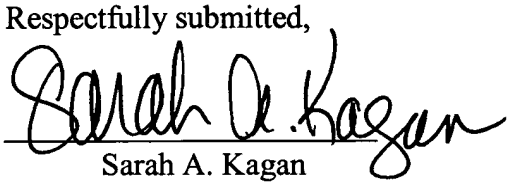
The claims have been amended to recite a particular nucleotide analog moiety, a particular tether, and specific portions of each which are linked to each other. All component parts of the claimed bisubstrate inhibitors were known. One of skill would merely need to assemble the parts using the linkages recited in claims 1 and 60, and taught in the specification. Such assembly would be routine and not require undue experimentation.

One of ordinary skill in the art could practice the invention readily without recourse to extensive experimentation, and certainly without recourse to undue experimentation.

New claims 77-88 do not recite a peptide which is a substrate for a kinase, but simply recite a peptide. Because the inhibitors comprise a known substrate moiety of kinases, ATP, they are inherently inhibitors of kinases. The peptide, depending on its composition, may provide additional potency or specificity to the bisubstrate inhibitor. It is respectfully submitted that the genus of peptides is adequately enabled.

Respectfully submitted,

Dated: February 28, 2005

By: 

Sarah A. Kagan
Reg. No. 32,141

Banner & Witcoff Ltd.
Customer No. 22907